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Highly efficient one-pot C-, N- and O-acylation of indolin-2-one analogs

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ABSTRACT

A highly efficient one-pot multiple acylation at chemically non-equivalent sites on indolin-2-one and related motifs using 4-(*N,N*-dimethylamino)pyridine as a catalyst is described. This procedure gives extremely facile entry to highly desired 3-acyl-2-hydroxy-indole synthons among other derivatives.

The indole core is a prevalent substructure in many natural products and biologically active compounds.[1] Owing to its biological importance, indole-based compounds attract special attention as building blocks for the development of therapeutic agents by medicinal chemists.[2,3] Furthermore, many indole-based alkaloids also serve as naturally occurring plant protecting agents, such as phytoalexins.[4] The interesting and remarkable bioactivity surrounding the indole moiety continues to be a vector in the development of new methodologies to find useful compounds. Thus, the need for the development of efficient and practical syntheses of indoles bearing a variety of substitution patterns is of great significance. The indolin-2-one (**1**) moiety serves as a useful starting compound in the synthesis of many indole-based molecules.[5,6] Our research group derives substantial capability in the chemistry of indole-based naturally occurring and synthetic bioactive molecules through previous experiences.[6,7] Building on this evolving expertise, our research team is actively involved in exploring the reactivity of indolin-2-ones and its application in the synthesis of biologically relevant compounds. Acetylation of indolin-2-one (**1**) using acetic anhydride is well documented in the literature,[8] however, a one-pot multiple acetylation on this framework is unprecedented. Herein, we wish to report a highly efficient one-pot carbon-, nitrogen- and oxygen-acylation on indolin-2-one motifs. Similar acetylation reactions on 1-alkylindolin-2-ones, indoline-2-thione and 1-methylindoline-2-thione resulted in one-step syntheses of multi-acetylated and/or chemoselectively mono-acetylated products.

Our investigation led to a facile and efficient synthesis of 3-acetyl-1-alkyl-2-hydroxyindoles among other synthetically useful indole derivatives. Several 3-acetyl-1-alkyl-2-hydroxyindoles have been prepared previously in three steps using substituted anilines as starting compounds.[9,10] In these cases, the anilines were first treated with a diketene to give intermediate 3-oxo-*N*-alkyl-*N*-arylbutanamides, which upon reacting with tosyl azide and a base resulted in 2-diazo-3-oxo-*N*-alkyl-*N*-arylbutanamides (Scheme 1). The 2-diazo-3-oxo-*N*-alkyl-*N*-arylbutanamides, in the presence of 5 mol % $Rh_2(OAc)_4$, in benzene produced 3-acetyl-1-alkyl-2-hydroxyindoles. Furthermore, while working towards the synthesis of (+)-yatakemycin, Boger and co-workers have reported chemoselective S-acetylation of complex indoline-2-thione in 77% yield by using acetic anhydride;[11] our investigation also reports a similar observation (vide infra). In another synthetically demanding endeavour, aromatic *o*-stannylmethylated isothiocyanates have been used to prepare S-acylated 2-mercaptoindoles.[12]

The use of acetic anhydride for heteroatom acetylation is quite common but there are relatively few reports known that describe its use in C-acetylation unaided by Lewis acids. For instance, the preparation of 3-acetoxy-2-acetylbenzofuran from 2-(2*H*)-benzofuranone under acidic conditions was reported by Bergman and Egestad.[13] Simig and co-workers have demonstrated the use of DMAP (1.1 equiv) and an acyl chloride for C-acylation step in the synthesis of tenidap, an antirheumatic drug developed by Pfizer.[14]

As mentioned previously, indolin-2-ones have been converted to the corresponding *N*-acetyl derivatives using acetic anhydride under

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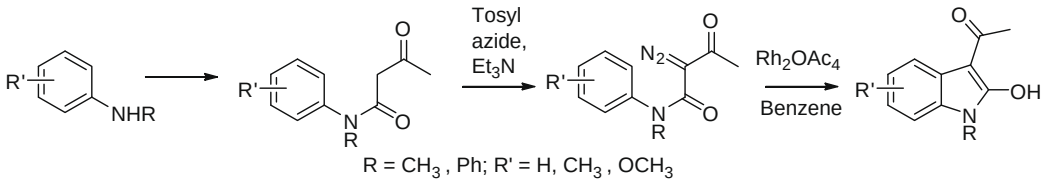


Scheme 1. Synthesis of 3-acetyl-2-hydroxyindoles[9,10]

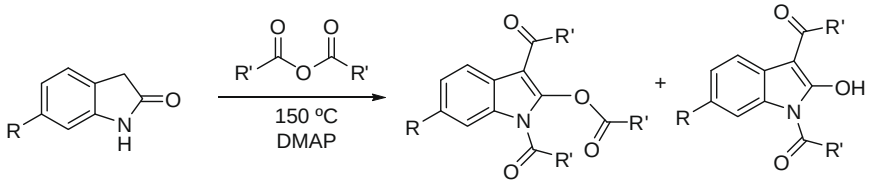
reflux conditions.[8] Reports in the literature and our own experience suggest that this acetylation proceeds quite slowly. The reaction generally requires 16–72 h for completion. In order to accelerate the reaction rate we decided to use a catalyst (DMAP) for the acetylation reaction. DMAP is a general catalyst well known to catalyze acylation, alkylation, carbonylation, dehydration, esterification, nucleophilic substitution, etc. reactions involving a variety of functional groups.[15] Indeed, the use of 1 mol % of DMAP in the acetylation reaction on indolin-2-one (**1**) increased the reaction rate significantly.[16] A thin layer chromatography (TLC) analysis revealed quantitative conversion to a single product in just 4 h. However, the spectroscopic analysis of the isolated product indicated that more than one acetylation had taken place on the indolin-2-one moiety. In fact, three sites viz. –*N*, –*O* and 3-*C* of indolin-2-one (**1**) appeared to have been acetylated in this single pot reaction.[17] We decided to systematically investigate the scope of this unique tri-acetylation reaction in detail using indolin-2-one analogs and related compounds with a variety of acyl anhydrides. The results summarized in Table 1 indicate that the acetylation of 6-chloroindolin-2-one (**2**) under similar reaction conditions also provided a tri-acetylated product **4a** in quantitative yield but the reaction time was reduced to 1 h. The work-up[16] for both the reactions (**1** and **2**) was relatively straightforward; the excess of acetic anhydride was evaporated under reduced pressure and the residues obtained were recrystallized using methanol to give pure products. Furthermore, the reactions of **1** with other anhydrides namely propionic and butyric anhydrides (Table 1, entries 3 and 4) resulted in a mixture of tri- (**3b**,**c**) and di- (**5b**,**c**) acylated products, the latter being the major products. Because of high boiling nature of propionic and butyric anhydrides, a work-up procedure similar to the one used for **1** and **2** was not easily amenable to remove the excess of anhydrides from the reaction mixture. The reaction mixture was purified by partial removal of acyl anhydride in vacuo and column chromatography to obtain 1,3-diacyl-2-hydroxyindoles (**5b**,**c**) as major products (Table 1). Isolation of the **5b** and **5c** as major products appears to be a deviation from the exclusive triacylation witnessed in case of acetylation reactions of compounds **1** and **2** (Table 1, entries 1 and 2). This deviation could have resulted from steric bulk imparted by longer chain acyl groups. We plan to study this phenomenon in detail in the near future.

The catalytic efficiency of DMAP for tri-acetylation can be explained as follows: the *N* of indole being the most nucleopilic[8] likely gets acetylated first. Subsequently, the presence of electron-withdrawing acetyl group on *N*-1 position assists in the second acetylation at *C*-3 of indole. The unique 1,3,5-tricarbonyl system formed as a result, forces the acetylation of *C*-2 oxygen last in this sequence of multiple acetylation.

After determining the generality of the reaction using a range of acyl anhydrides we decided to restrict our study to acetic anhydride and the use of various N-substituted indolin-2-ones (**7–12**) which were synthesized following the previously published procedures.[8,18] Compounds **7**–**12** were subjected to acetylation reaction in the presence of DMAP as described above. The catalytic acetylation of 1-alkylindolin-2-ones (**7**–**10**) resulted in the formation of corresponding 3-acetyl-2-hydroxy derivatives (**16–19**) in good yields (Table 2). It was interesting to note that C-monoacetylated compounds, rather than expected O- and C-diacetylated products, were exclusively formed. At this point, efforts were not made to force O-acetylation by increasing the reaction time and/or applying more heat. Formation of 3-acetyl-1-alkyl-2-hydroxyindoles (**16**–**19**) in good yields from easily available starting materials and a very simple and inexpensive reaction procedure is a significant improvement to the previously reported three-step synthesis of compounds of this type involving explosive diazo compounds and expensive Rh catalyst.[9,10] Mono-C-acetylation rather than di-C- and O-acetylation in case of N-alkylated indolin-2-ones can be explained, at least in part, due to the electron-donating nature of N-alkyl groups which reduces the nucleophilicity of the chelated enolic hydroxyl group. When electron-withdrawing N-acetyl substituted indolin-2-ones **11** and **12** were reacted under similar conditions, the tri-acetylated products **3a** and **4a** were obtained in excellent yields (Table 2, entries 5 and 6).

To further expand the substrate scope of the reaction, synthetically accessible indoline-2-thiones[6] **13** and **14** and commercially

Table 1
Reaction data for multiple acylation on indolin-2-ones **1** and **2**



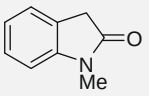
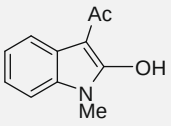
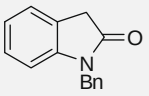
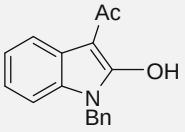
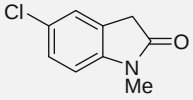
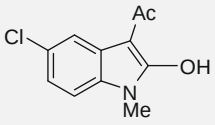
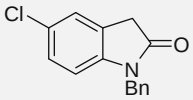
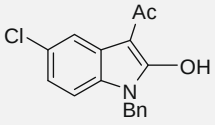
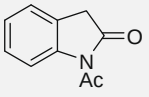
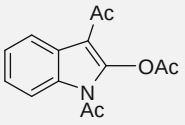
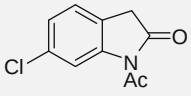
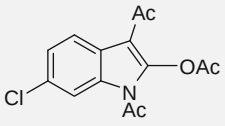
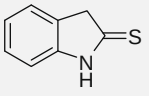
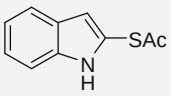
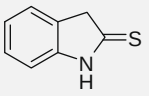
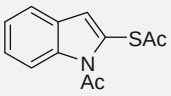
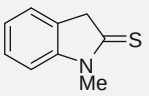
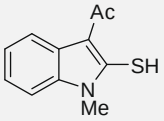
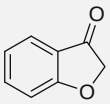
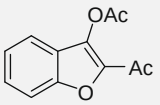
1 R = H
2 R = Cl

3 R = H
4 R = Cl

5 R = H
6 R = Cl

Entry	Substrate	Anhydride (R')	Reaction time (h)	Product **3**/**4** (% yield)	Product **5**/**6** (% yield)
1	**1**	Me	4	**3a** (95)	**5a** (<5)
2	**2**	Me	1	**4a** (93)	**6a** (<5)
3	**1**	Et	4	**3b** (<5)	**5b** (76)
4	**1**	Pr	4	**3c** (<5)	**5c** (82)

Table 2
Reaction data for acetylation on 1-substituted indolin-2-ones (**7**–**12**), indoline-2-thiones (**13**,**14**) and benzofuran-3-one (**15**)

Entry	Substrate	Product	Reaction time (h)	Product (% yield)
1	 **7**	 **16**	4	81
2	 **8**	 **17**	1	75
3	 **9**	 **18**	4	78
4	 **10**	 **19**	4	80
5	 **11**	 **3a**	4	94
6	 **12**	 **4a**	4	90
7	 **13**	 **20**	1	94
8	 **13**	 **21**	4	78
9	 **14**	 **22**	2	71
10	 **15**	 **23**	1	90

available benzofuran-3-one (**15**) were treated with acetic anhydride in the presence of 1 mol % DMAP. The reactivity of thione **13** was found to be somewhat different than indolin-2-ones (**1**,**2**). The TLC analysis revealed that the thione **13** was completely consumed within one hour of the reaction. However, the spectroscopic analysis of the product indicated that only S-acetylation had taken place and compound **20** (S-acetylated 2-mercaptoindole) was isolated in excellent yield (Table 2, entry 8). Heating for an additional 3 h resulted in the formation N,S-diacetylated product **21** in good yield (Table 2, entry 9) but no C-acetylated product was isolated from the reaction mixture. While the absence of C-acetylation in this case initially appeared surprising but upon close inspection it was discerned that the higher nucleophilicity of the *S* atom is responsible for this. Subsequent acetylation occurred at *N*- which is next in the order of nucleophilicity. After the N- and S-diacetylation, the nucleophilicity of the 3-*C* was lost and therefore no further acetylation occurred under the applied reaction conditions. On the contrary, the N-methyl substituted thione **14** reacted with acetic anhydride in fashion similar to *N*-alkylindolin-2-ones (**7–10**), giving rise to the 3-acetyl-2-mercapto product **22** in 71% yield. This observation is consistent with the effect of electron-donating N-alkyl group on the nucleophilicity of *S*/*O* on the neighbouring *C*-2 carbon (vide supra). The reaction results indicate that the electron-donating ability of N-methyl group becomes detrimental to the nucleophilicity of *S* at *C*-2. With the thione S unacetylated, the *C*-3 carbon remains nucleophilic enough to undergo acetylation. We will continue to investigate this aspect.

Acetylation occurred at both *C*-2 and *C*-3 *O*-positions in the case of **15** to produce compound **23** and the reaction time was also found to be substantially shortened (1 h); in the literature diacetylation of **15** to produce the same product uses stirring in acetic anhydride and sulfuric acid for 5 h at room temperature.[13]

In conclusion, we have described first one-pot multiple acylation of indolin-2-ones, indoline-2-thiones and benzofuran-3-one using catalytic amount of DMAP and acyl anhydrides. Indolin-2-ones devoid of N-alkyl substitution resulted in triacetylation at *N*-1, *C*-2 *O* and *C*-3 carbon. *N*-Methylindolin-2-ones, under identical conditions, furnished *N*-methyl-3-acetyl-2-hydroxyindoles as the major product. Indoline-2-thiones devoid of N-alkyl substitution underwent chemoselective monoacetylation on *S* after 1 h of reaction time; prolonged reaction time led to the formation of N- and S-diacetyl derivative. On the other hand, *N*-methylindoline-2-thione resulted in chemoselective monoacetylation at the *C*-3 position. The variance in chemistry witnessed here by subtle change in reactivity is quite interesting and warrants further investigation. The products obtained through this acylation study with unprecedented results are extremely valuable in preparing a large number of unexplored heterocyclic systems.

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16. In a typical procedure, indolin-2-ones (0.5 g, 3.76 mmol), acetic anhydride (3.8 g, 37.5 mmol) and 4-dimethylaminopyridine (DMAP, 1 mol %) were heated at 150 °C for 4 h in a round-bottomed flask equipped with air condenser and $CaCl_2$ guard tube. After the completion of reaction (as evident from TLC), the excess of acyl anhydride was evaporated under reduced pressure and residue was recrystallized using methanol to give **3a** as white solid (0.93 g, 95% yield). Mp: 137–139 °C (methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 8 Hz, 1H), 7.61 (d, J = 7.5, 1H), 7.34 (dd, J = 8, 8 Hz, 1H), 2.21 (dd, J = 8, 8 Hz, 1H), 2.74 (s, 3H), 2.72 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 167.8, 167.0, 161.8, 137.8, 129.1, 124.9, 122.9, 121.6, 116.3, 115.5, 27.0, 21.3, 19.0. FTIR ν_{max} (KBr): 3471, 1757, 1742, 1698, 1460, 748 cm^{-1}. GC–MS (EI): m/z (% relative abundance) 259 (M^+, 5), 217 (40), 175(100), 150 (35), 129 (10).
17. Spectroscopic data are given in Ref. [16].
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